URINARY CLARA-CELL PROTEIN IN KIDNEY TRANSPLANT PATIENTS AS MARKER OF PROXIMAL TUBULAR DYSFUNCTION

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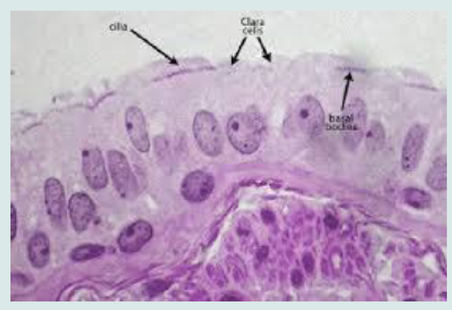
Clara Cell Protein (CC16) was first described by Max Clara in 1937. It´s a protein expressed primarily by the bronchial cells. It´s rapidly eliminated from circulation by glomerular filtration, reabsobed almost entirely and catabolized in proximal tubule cells. It shows a tubular management similar to other urinary markers as β2microglobulin (β2m), retinol biding protein or cistatin C. For this reason, it has been used by some authors as a good marker of proximal tubular dysfunction.

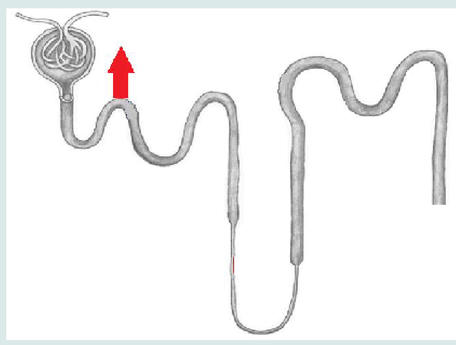
AIMS

- Analyze urinary elimination of CC16 in kidney transplant (KT) patients, compared with a healthy control group.
- Correlate urinary CC16 with other known markers of proximal tubular dysfunction, as β2m and N-acetylglucosaminidase (NAG).
- Evaluate the relation between these markers and the GFR at 4 years of follow-up.



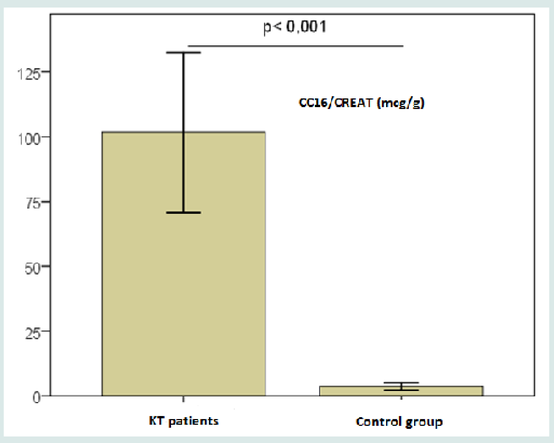
METHODS

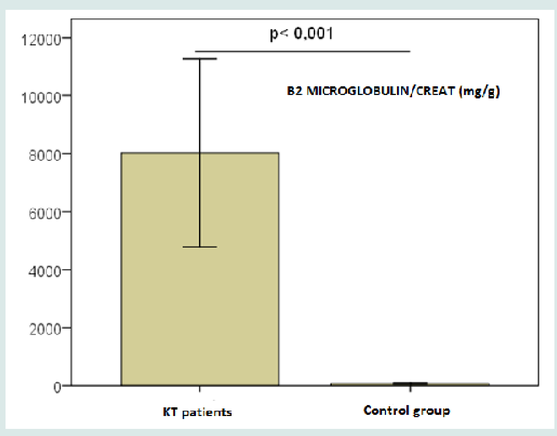
- Observational transversal study comparing urinary markers of a group of KT patients with a group of healthy controls.
- Urinary levels of the 3 markers and albumin were measured in both groups, and expressed as a ratio with urinary creatinine.
- Clinical, biochemical and drug features were collected.
- After 4 years of follow-up, correlation was made with renal prognosis.



RESULTS

- 110 KT patients were studied, 68% male, with age 51,6±12,3 years (21-79) and a duration of KT of 7,8±5,8 years The etiology of CKD was diabetes in 25%, glomerulonephritis in 17%, PKD and NAS 13% each. 25% had presented acute rejection before, and 8% of patients had chronic allograft dysfunction.
- 84% were on triple therapy (78% FK, 20% cyclosporin and 2% rapamycin).
- Control group was formed by 20 volunteers (12 male/8 female), mean age of 48,7±18,3 years.





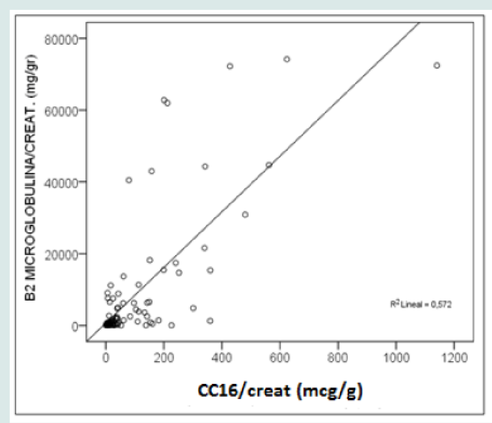
- Mean urinary levels of CC16 in KT patients were 100,9 ± 163 µg/g, significantly higher than the controls (3,6 ± 2,8 µg/g, p<0,001).
- Mean urinary levels of β2m and NAG were also significantly higher in KT patients (8,1 ± 16,6 vs 0,07 ± 0,05 g/g and 4,4 ± 3,7 vs 2,3 ± 1,2 U/g, respectively, p<0,001).
- We found high levels of CC16, β2m and NAG in 75, 81 and 30% of KT patients, respectively.
- Classifying patients by quartiles of GFR, we observed significant higher levels of CC16, β2m and NAG, as GFR decreases.
- In patients with GFR>60 ml/min we still found high levels of CC16, β2m and NAG in 61, 70 and 20% respectively.
- Diabetic patients had significant higher levels of CC16 compared with non-diabetic ones, as it ocurred with β2m and NAG, without differences in urinary albumin or serum creatinine.

MDRD (GFR) quartiles	1º Quartile (11-38 ml/min)			2º Quartile (38-51,1 ml/min)			3º Quartile (51,1-69,4 ml/min)			4º Quartile (69,4-142 ml/min)			P
	Mean	n	SD	Mean	n	SD	Mean	n	SD	Mean	n	SD	
β2m/creat (mg/gr)	20552,51	26	26017,66	7206,87	24	12703,57	2305,21	26	4424,88	2427,65	28	7646,12	**<0,001**
CC16/creat (µg/g)	212,62	27	260,98	93,89	27	115,22	49,42	28	65,47	54,27	28	88,53	**<0,001**
NAG/creat (U/gr)	5,55	26	4,47	5,06	28	3,40	3,86	28	3,68	3,40	28	2,89	**0,01**
ALB/creat (mg/g)	796,20	29	1489,57	115,29	29	194,23	64,71	29	128,34	98,53	30	254,44	**<0,001**

DIABETES MELLITUS	NO			YES			
	Mean	n	SD	Mean	n	SD	p
Creatinine (mg/dl)	1,51	89	0,75	1,44	30	0,40	0,56
β2m/creat (mg/gr)	5947,78	77	14425,89	13972,61	27	20961,17	**<0,001**
CC16/creat (µg/g)	91	80	169	130	30	147	**0,02**
NAG/creat (U/gr)	3,86	81	3,44	6,12	29	3,93	**<0,001**
ALB/creat (mg/g)	277,99	88	891,93	234,58	29	503,43	0,24

- CC16 has a positive correlation with urinary β2m (r=0,76, p<0,001), urinary albumin (r=0,68, p<0,001) and urinary NAG (r=0,29, p<0,005).
- Urinary levels of CC16 and β2m were associated with a lower GFR at 4 years of follow-up (r=-0,316, p<0,05 and r=-0,27, p<0,05), even with a slightly higher association than urinary albumin (r=-0,23, p<0,05)).
- Patients that had initiated dialysis at the end of the study, had presented higher levels of CC16 and β2m at the beginning of the study (275,5 ± 642,9 vs 75,4 ± 104,5 µg/g, p<0,05 and 25,2 ± 30,2 vs 5,5 ± 12,1 g/g, p<0,05).

CC16/creat (µg/g)		β2m/creat (mg/gr)	ALB/creat (mg/g)	NAG/creat (U/gr)	MDRD (ml/min)
	Pearson correlation	0,76**	0,68**	0,29**	-,409**
	Sig. (bilateral)	<0,001	<0,001	<0,001	<0,001
	N	99	109	105	110



Conclusions

- This is the first report of urinary CC16 protein in KT patients and it shows a good relation with other markers of proximal tubular dysfunction.
- Urinary CC16 can be used as a new marker of proximal tubular dysfuncion in KT.
- Urinary β2m and CC16 are asocciated with a worse GFR at 4 years of follow-up. Monitor urinary markers of proximal tubular dysfunction as β2m and CC16 can predict renal prognosis.
- Proximal tubular dysfunction is very prevalent in KT patients.

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